Comparison of SSRI and SNRI on Their Effects of Relieving Major Anxiety

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Abstract

Anxiety disorders, including generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder, and phobia-related disorders are the most common group of mental disorders in the U.S. Anxiety disorders are treated with psychological therapy and pharmacotherapy. Pharmacotherapy includes first-line drug selective serotonin reuptake inhibitors (SSRIs) as well as second or third-line drug serotonin-norepinephrine reuptake inhibitors (SNRIs). Both have the potential to induce adverse effects and can lead to similar withdrawal symptoms due to their effects on neurotransmitters and serotonin levels (Gupta et al., 2021). However, SSRI is widely considered to be the first choice for anxiety disorder therapy in comparison to SNRI because of its recent developments.

Introduction

Common anxiety disorders are often associated with the hypothalamus-pituitary adrenal system (HPA axis). The HPA axis controls responses to stress. The HPA axis causes an increase in cortisol secretion to the adrenal cortex, increasing the level of salivary cortisol. When the level of salivary cortisol increases, individuals will experience an increase in stress and anxiety levels. Promotion for anxiety disorders is influenced by genetic, epigenetic, and other environmental factors, while the severity of these psychiatric disorders are often underestimated and underrecognized by society. GAD and PD are among the most prevalent mental health diseases in the United States, and they can negatively impact a patient's quality of life and interfere with essential activities of daily lives. For instance, GAD and PD have been associated with a loss in motivation, as well as a loss in the ability to learn, memorize, and make decisions. According to a study conducted by Front Public Health, the 12-month prevalence for GAD and PD among U.S. adults 18-64 years of age is 2.9-3.1% (Bandelow et al., 2017). Patients with GAD are typically presented with pervasive anxiety and worry that are associated with symptoms like irritability, fatigue, sleep disturbance, and difficulty concentrating. However, PD is characterized by recurrent panic attacks along with other physical symptoms such as accelerated heart rate, trembling, and nausea or abdominal distress (Roy-Byrne et al., 2006).

In 1988, the first SSRI fluoxetine was introduced in the United States. It was discovered that highly receptor-sensitive agents would lead to a superior side effects profile, especially compared to that of first-generation antidepressants, such as tricyclic antidepressants (TCAs). TCAs have high efficacy but fatal side effects. The discovery of SSRIs was an important step in the treatment of depression and anxiety disorders because of their high sensitivity to serotonin receptors and low propensity to cause seizures (Lambert & Bourin, 2002). Currently, fluoxetine and sertraline are the most commonly prescribed SSRIs in the United States and will be used as representative SSRIs in this study.

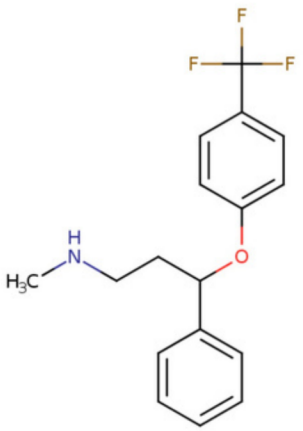
In 1993, venlafaxine immediate release (IR) was the first SNRI in the United States that was approved by the United States Food and Drug Administration (FDA). This was followed by a micro-encapsulated extended release (XR) formulation, which was presented to have milder effects. IR Venlafaxine is developed to dissolve without delaying absorption of the drug while XR Venlafaxine is designed to release in a controlled manner during an extended period following ingestion. Venlafaxine is widely used in the treatment of major depression, GAD, PD, and phobia-related disorders. Other SNRIs, such as duloxetine, desvenlafaxine, milnacipran, and levomilnacipran, exhibit different structures than venlafaxine and are mainly used in treating major depression and GAD. At present, two SNRIs are used in clinical trials, including the venlafaxine and milnacipran. Both venlafaxine and milnacipran will be the subject SNRIs of this study.

Description of SSRI and SNRI

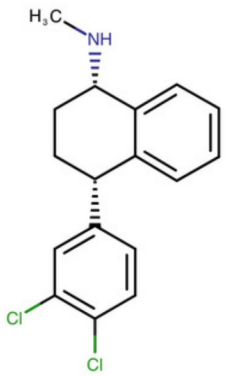
1. Chemical Properties.

SSRI:

Fluoxetine (C17H18F3NO): Fluoxetine is classified as a diphenhydramine, an antihistamine and sedative mainly used to treat allergies. Fluoxetine is a trifluoromethyl benzene, a trifluoromethane with a substituted phenyl group. Its metabolite, norfluoxetine, is freely soluble in methanol and ethanol, with a melting temperature of 158.4-158.9ºC (Drug Bank, 2022).

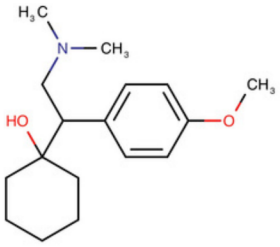


Sertraline (C17H17Cl2N): Sertraline is classified as a tetralin, with a methyl amino substituent at position 1 and a 3,4-dichlorophenyl group at position 4. [6] A tetralin is a partially hydrated naphthalene derivative. Desmethylsertraline, the active metabolite of sertraline, has a melting temperature of 243-249ºC (Drug Bank, 2022).

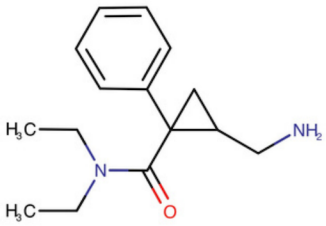


SNRI:

Venlafaxine (C17H27NO2): Venlafaxine is classified as both a tertiary alcohol and amino. Its basic structure is an N,N-dimethylethylamine, with a substituent at position 1. The substituent at position 1 contains both a 1-hydroxycyclohexyl and 4-methoxyphenyl group. The active metabolite of venlafaxine is O-desmethylvenlafaxine (ODV), which has a melting temperature of 208-213ºC (Drug Bank, 2022).



Milnacipran (C15H22N2O): Milnacipran is a member of the acetamides and is classified as a monocarboxylic acid amide Milnacipran undergoes minimal hepatic metabolism (Drug Bank, 2022).



2. Synthesis of SSRI and SNRIs

Chemical synthesis is the preparation of an organic compound that can be produced from inexpensive and widely available start materials. Biosynthesis involves the synthesis of complex molecules that undergo multiple steps of production. Most molecules that require synthesis by plants, microbes, or biotechnology are biosynthesized. Both the SSRIs (fluoxetine and sertraline) and SNRIs (venlafaxine and milnacipran) in this study are all chemically-synthesized due to their chemical structures and mechanism (Dell'Osso et al., 2010).

Fluoxetine: Fluoxetine has been synthesized through different methods, including one that begins with a Mannich reaction of acetophenone with paraformaldehyde and methylamine to produce dimethylaminopropiophenone (Drug Summary, 2022). This is followed by the reduction of the carbonyl group of the dimethylaminopropiophenone, which produces an alcohol. The nucleophilic substitution of the resulting hydroxyl group from the last reaction with thionyl chloride produces 3-chloro-3-phenylpropan-1-amine. Then, 3-chloro-3-phenylpropan-1-amine is treated with sodium hydroxide and 4-(trifluoromethyl)phenolate to form a secondary amine, which will be demethylated by cyanogen bromide and potassium hydroxide to produce fluoxetine (Pinna, 2015).

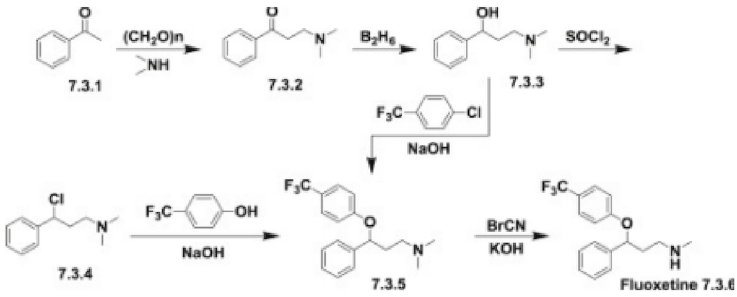


Figure 5. The Approach Synthesizing of Fluoxetine

Sertraline: The original approach of sertraline synthesis involved a five-step reaction that can be replaced by the one-step condensation of α-naphthol with O-dichlorobenzene in the presence of AlCl3. This produces a substituted tetralone, which is further condensed with methylamine in the presence of TiCl4 to form an imine (Murdoch et al., 1992). During the reaction, an equal ratio of rac-cis and rac-trans-amines will result from the reduction of the imine double bond. The addition of D(-)-mandelic acid will result in the production of sertraline.

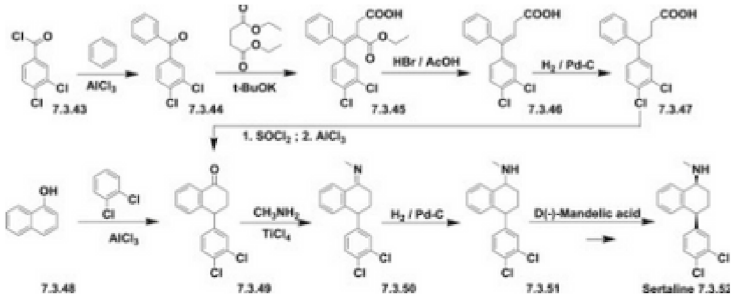


Figure 6. The Approach Synthesizing of Sertraline

Venlafaxine: Venlafaxine is first synthesized by the nucleophilic addition of 4-methoxyphenyl acetonitrile with cyclohexanone, using BuLi or LDA. The intermediate then undergoes a catalytic hydrogenation with the aid of a metal catalyst, Rh or Al2O3, to give (RS)-1-[2-amino-1-(4-methoxyphenyl) ethyl]-cyclohexanol. The cyclohexanol will then be dimethylated to produce venlafaxine by reductive amination, using the Eschweiler-Clarke procedure. (Savella, 2023)

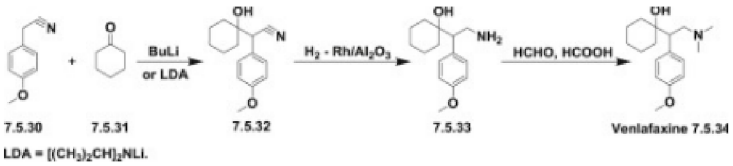


Figure 8. The Approach of Synthesizing Venlafaxine

Milnacipran: The synthesis of milnacipran starts with the treatment of compound 2 with AlCl3 and diethylamine at room temperature. This results in the opening of the ring and the production of an alcohol that is oxidized with Dess-Martin periodinane (DMP) (Savella, 2021). Acetic acid or aqueous ammonium in addition to cyanoborohydride, ethyl acetate, and hydrochloric acid are then added to increase the chemoselective reductive amination of aldehyde (Vukics et al., 2001).

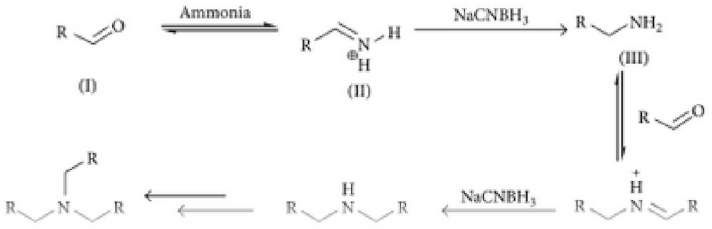


Figure 9. The Approach of Synthesizing Milnacipran

3. Mechanism of Action and Metabolism

It is speculated that the cause of various anxiety disorders is the deficiency in serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter that influences autonomic function, modulation of mood, recognition, and hormone secretion. Serotonergic neurons mediate anxiety responses. These neurons are located in the raphe nuclei, a part of the brainstem which releases serotonin to the brain.

SSRI, as its name suggests, inhibits the reuptake of serotonin specifically, increasing the availability of serotonin in the synaptic cleft without interfering with other neurotransmitters. Fluoxetine, like the other SSRIs, acts to block the sodium-dependent serotonin transporter (SLC6A4) at the presynaptic axon terminal, thereby increasing the levels of 5-HT. Upon ingestion, fluoxetine is metabolized to norfluoxetine by enzymes via N-demethylation. Additional enzymes will mediate O-dealkylation of fluoxetine and norfluoxetine, which will eventually metabolize into hippuric acid. Similarly, sertraline, the other representative SSRI, undergoes N-demethylation to form N-desmethylsertraline (Marsh, 2007). However, the metabolism of sertraline also involves N-hydroxylation, oxidative deamination, and glucuronidation. Sertraline binds to human serum albumin with high affinity via hydrophobic interactions and hydrogen bonding. Its metabolic activity happens mainly in livers (Desireddy et al., 2017).

SNRIs, in contrast to SSRIs, elevate the levels of both serotonin and norephedrine. This alleviates the symptoms of anxiety disorders and other diseases such as major depression and obesity. SNRIs act upon serotonergic and noradrenergic neurons without acting upon histaminergic receptors. Venlafaxine, one of the representative SNRIs in this study, functions by increasing the levels of serotonin, norepinephrine, and dopamine by blocking the reuptake at the presynaptic terminal by transport proteins (Zoloft, 2023).

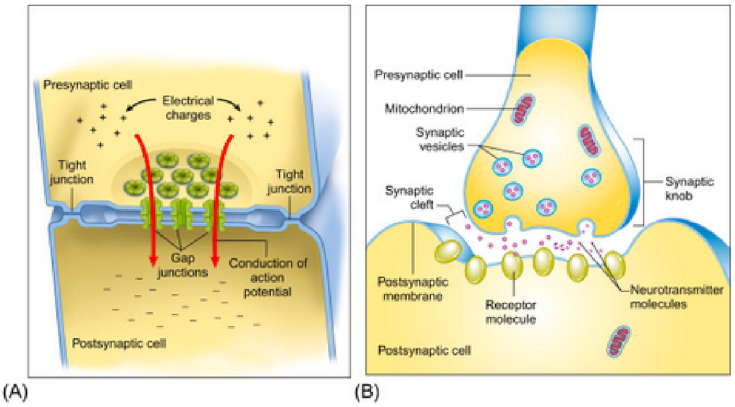


Figure 10. The Reaction of SSRI at Synaptic Axon Terminal

Unlike other SNRIs, venlafaxine is more potent in inhibiting the reuptake of serotonin than the reuptake of norepinephrine. After oral administration, venlafaxine is well-absorbed from the gastrointestinal tract and, similar to the SSRI sertraline, and undergoes extensive hepatic metabolism. It primarily undergoes CYP2D6-mediated demethylation to form ODV. Milcipran, the other SNRI in this study, functions by inhibiting the reuptake of 5-HT and norepinephrine. Upon administration, milnacipran undergoes desethylation and hydroxylation to form N-desethyl levomilnacipran and p-hydroxy-levomilnacipran. Both are oxidative metabolites of milnacipran and will undergo conjugation with glucuronide to form the conjugate milnacipran carbamoyl-O-glucuronide (EffectorXR, 2021).

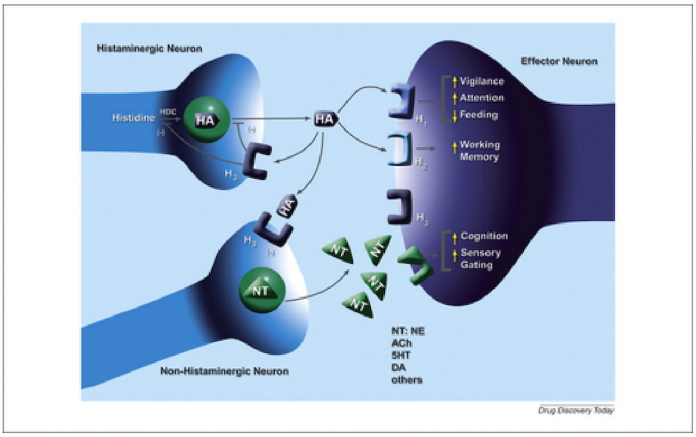


Figure 11. The Reaction of SNRI at Histaminergic Receptors

4. Mode of Delivery and Dosage

Drugs can be delivered to the human bodies in different routes to achieve the highest efficacy. The mode of delivery primarily depends on the half-life, toxicity, and mechanism of action of the drug. On the other hand, the dosage is associated with the medical condition, weight, and response of the patient.

Fluoxetine : Generally, fluoxetine should be administered once per day, between 20 to 40 mg. However, considering both efficacy and adverse effects, it is possible for the drug to be administered at smaller doses, like 10 mg for individuals

with low tolerability of side effects. Inversely, individuals may require high doses of 60-80 mg for effective medication. Delayed-release capsules, medications that are designed to release the active ingredient after an extended period of time following the administration, are generally administered at 90 mg per week and are comparable in efficacy with the daily 20 mg treatment. Fluoxetine, compared with other SSRIs, has milder withdrawal symptoms, including sleep impairment, fever, and nausea. In addition, drug-drug interaction should also be strictly monitored as non-steroid inflammatory agents might affect the efficacy of fluoxetine (Pae et al., 2009).

Table 1. The Mode of Delivery and Dosage of Major Brands of Fluoxetine

Drug	Type	Dosage	Intake method
Prozac	Capsule	10 mg/20 mg/40 mg	Oral
Rapiflux	Delayed-release capsule	90 mg	Oral
Sarafem	Tablet	10 mg/20 mg/60 mg	Oral
Selfemra	Solution	20 mg/5 mL	Oral

Sertraline: Generally, sertraline is administered once per day, either in the morning or evening, starting with the initial dosage of 50 mg to a maximum dosage of 200 mg (Drug Bank, 2023). Single and multiple oral doses of 50 to 200 mg per day have been well-tolerated in patients with anxiety disorders according to clinical trials conducted by FDA.

Table 2. The Mode of Delivery and Dosage of Major Brands of Sertraline

Drug	Type	Dosage	Intake method
Sertex	Tablet	25 mg/50 mg/100 mg	Oral
Zoloft	Capsule	150 mg/200 mg	Oral
Zoloft	Solution	20 mg/1 mL	Oral

Venlafaxine: Venlafaxine is prescribed only for individuals over 18 years old and should be taken with food for better absorption. Immediate-release tablets can be cut and crushed but extended-release tablets cannot. Treatments by venlafaxine generally start between 75 to 150 mg per day, with an upper dose of 375 mg per day, divided into three doses (PubChem, 2023).

Table 3. The Mode of Delivery and Dosage of Major Brands of Venlafaxine

Drug	Type	Dosage	Intake method
Effexor XR	Extended-release tablet	25 mg/37.5 mg/50 mg/75 mg/100 mg	Oral
Xanax	Immediate-release tablet	37.5 mg/75 mg/150 mg/225 mg	Oral

Milnacipran: The dose range of milnacipran is 50-200 mg in divided doses. Treatments by milnacipran begin at 25 mg per day and can be increased to the maximum of 200 mg according to individual need and response (Pae et al., 2009). Like venlafaxine, the other SNRI, milnacipran, is also recommended to be taken with meals and there are no dose-dependent adjustments that can be made for patients with hepatic impairment and chronic liver disease. In order to minimize withdrawal effects, milnacipran should be tapered after extended use and should not be discontinued abruptly.

Table 4. The Mode of Delivery and Dosage of Major Brands of Milnacipran

Drug	Type	Dosage	Intake method
Joncia	Capsule	25 mg/50 mg/100 mg	Oral
Savella	Tablet	12.5 mg/25 mg/50 mg/100 mg	Oral

4. Adverse Effects

Due to SSRI selectivity on targeting serotonin reuptake transport proteins without interfering with other receptors, such as histaminic, cholinergic, dopaminergic, and noradrenergic receptors, SSRIs are more tolerable for patients than other drugs that treat anxiety and depression, such as TCAs. [25] However, serotonin receptors mediate a variety of functions unrelated to mood, including appetite, sleep, and sexual function. SNRI inhibition of the reuptake of serotonin causes more of the available neurotransmitters to interact with the aforementioned receptors. The increased interaction of these receptors is closely associated with the adverse effects of SSRI. Common side effects developed by patients under SNRI treatment include headaches, gastrointestinal complaints, sleep impairment, and sexual dysfunction. Most SSRI side effects are dose-dependent and can usually be alleviated by reducing the dose. Like SSRI, patients treated with SNRI show a lower rate of treatment discontinuation than TCA, but many patients still experience various side effects including sexual dysfunction and elevation of blood pressure, especially in case of venlafaxine. A meta-analysis of 16 randomized controlled trials conducted by the Health Psychology Research in 2021 reported that milnacipran showed fewer adverse effects and lower premature withdrawal rates (Gupta et al., 2021).

Conclusion and Future Prospect

Currently, SSRI-related therapy is held to be the major treatment for patients with anxiety disorders. However, it could not be regarded as ideal because of its mild but still present side effects in addition to its poor cost-effectiveness. SNRIs, on the other hand, are receiving an increasing amount of consideration. A potential advantage of SNRI over SSRI is its selective inhibition on both serotonin and norepinephrine. However, it is still premature to acknowledge the superiority of SNRI over SSRI as anxiety disorders are often complicated by the presence of comorbid conditions. Therefore, this conclusion requires more meta-analyses to elucidate the data.

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